AMENDMENTS TO THE DRAWINGS

Attached hereto are replacement drawings sheets corresponding to FIGS. 4, 5c, 6c and 27 (sheets 4/38, 6/38, 8/38 and 29/38, respectively).

The following changes to these drawings have been made and are present in the replacement sheets:

FIG 4: The drawing has been labeled with "A" and "B" in correspondence with the brief description of FIG. 4.

FIGS. 5c & 6c: Italian words have been replaced with English words.

FIG. 27: The photomicrograph panels have been oriented properly.

No other changes to these sheets of drawings have been incorporated. No new matter has been added.

REMARKS

1. Appearance of New Counsel:

Pursuant to the provisions of 37 CFR 1.34, the undersigned attorney states that he is authorized to act on behalf of the applicant in this matter. Corresponding Revocation and New Power of Attorney and Change of Correspondence Address forms could not be executed in time to file along with this Submission, but will be provided as soon as possible.

2. Status Information:

Claims 1, 3-9, and 11-19 are pending, were examined, and were rejected. The previous rejection under 35 USC 102(b) on the basis of Piccioli et al. was withdrawn. Claims 1, 8, 11-16 and 19 have been amended and claims 3-7, 9, 17 and 18 have been cancelled in this paper. New claims 38-45 are presented.

The Office Action has been thoroughly considered. The objections, rejections and other requirements contained in the Office Action are each separately addressed in numbered paragraphs 4-14, below.

3. Amendments to the Claims and Support Therefor:

Claims 1, 8, 11-16 and 19 have been amended. New claims 38-45 are presented.

The amendments to claim 1 more particularly point out and distinctly claim the subject matter which applicants regard as their invention. The introduction of language limiting the claim to a transgenic mouse is fully supported by the entirety of the specification. The introduction of language indicating that the transgenic mouse has a genome comprising transgenes encoding a variable heavy chain and a variable light chain of an anti-NGF antibody, said transgenes being detectably expressed in the mouse by 90 days postnatal, is supported by the entirety of the specification and, for example, the disclosures on: page 7, lines 14-16; Example 1, page 26, lines 9-18; and, FIGS. 1 and 2. The introduction of the listed phenotypic characteristics is supported throughout the specification, and in particular, by the disclosures contained in the Detailed Description (see, for example, page 7, line 19 through page 8, line 7, and Table 1 on pages 9-11), the Examples (see Example 2, beginning on page 27, and related figures; and Example 3, beginning on page 37, and related figures), and by the previously pending claims.

Dependent claim 8 has been amended to be in accordance with amended claim 1, and specifies that the neurodegenrative pathology recited in claim 1 is present in the aged transgenic mouse (15 to 18 months postnatal, see page 27, line 5). Support for these amendments may be found, for example, in Examples 2 and 3 and the related figures (i.e., FIGS.11, 13, 16, 18, 20-22, 25, 26, and 28-30).

Claims 11 and 12 have been amended to correspond to the amendments made to claim 1.

Claim 13 has been amended to correspond to the amendments made to claim 1, and to clarify language.

Claim 14 has been amended to depend from and be consistent with new claim 38, which is supported by the entirety of the specification and the claims as filed, and in particular, by Examples 1 and 3.

Claim 15 has been amended to be consistent with the amendments to claims 1 and 14.

Claim 16 has been amended to be consistent with the amendments to claims 1 and 15.

Claim 19 has been amended to be consistent with claim 1.

New claim 38 is discussed above.

New claims 39-45, which depend from amended claim 1, are directed to tissue and fluids obtained from the transgenic mouse of claim 1, all of which may be directly derived from the transgenic mouse of claim 1 using routine procedures well known in the art, and are therefore supported by the instant specification. Obtaining the claimed tissues and fluids is well within the level of ordinary skill in the art, and the specification provides working examples which involve and describe the isolation of such tissues and fluids.

4. Requirement for Verification and Certification of Priority Documents:

As required by the Office, submitted herewith are replacement copies of the English translations of the Italian priority documents, as follows:

(i) A complete original copy of a sworn English translation of priority document RM2000A000306 (referred to by the Office as "RMA000306"),

prepared and sworn by Maria Antonietta Botti of the Italian Ministry dell'Economia e delle Finanze (which copy includes Ms. Botti's signature on each page as well as the Ministry's official stamp throughout the document), provided together with the Italian language version of the document so translated, as is the practice of the certifying authority. The undersigned attorney is advised by instructing patent counsel in Italy that this official sworn copy swears that the translation is complete and faithful.

(ii) A complete copy of a verified English translation of priority document MI99A001783, prepared and verified by Nicoletta Iaia, provided together with the Italian language version of the document so translated, and a VERIFICATION OF TRANSLATION by the translator.

Applicants respectfully submit that these translations satisfy the Office's conditions and requirements, and are otherwise in accordance with the Rules.

5. Objections to the Specification:

Objections to the Specification have been corrected in accordance with the examiner's requirements, as detailed below:

(i) The brief description of Figure 1 has been amended to include a description of panel F. No new matter has been added.

(ii) The brief description of Figure 16 has been amended to include a description of panel C. No new matter has been added.

6. Objections to the Claims:

All objections to the Claims have been corrected in accordance with the examiner's requirements, as detailed below:

(i) Claim 1 was objected to because it referred to *anti-NGH* rather than *anti-NGF*. This error has been corrected in amended claim 1. Claim 1 was also objected to on grammatical grounds. This error has been obviated by the amendments made to claim 1.

(ii) Claim 12 was objected to because of a failure to comply with Rule 121. The Listing of Claims presented herein is compliant with the Rules.

7. Compliance with Sequence Rules:

The examiner has required a replacement Sequence Listing that corrects various errors noted in the RAW SEQUENCE LISTING ERROR REPORT. In reply, applicants have submitted a replacement Sequence Listing, in paper and computer readable form, that corrects the noted , and sequence omission, in compliance with the Rules.

Applicants hereby state that the contents of the paper copy and computer readable copy of the Sequence Listing are identical and do not contain any new matter.

A amendment to the specification is made to append the identifier SEQ ID NO: 1 to the primer sequence shown on page 43, line 4 of the specification.

8. Rejections under 35 USC 112, 2nd paragraph:

Claims 4-9 and 14 were rejected under 35 USC 112, second paragraph, as being indefinite as specified.

Claims 4-7 and 9 have been cancelled, thus mooting the rejection as to these claims.

Claim 8 as amended, is dependent on amended claim 1, and the amendments to these claims obviate the rejection of claim 8.

Claim 14 has been amended, and now depends from new claim 38. The amendments clarify the point raised by the examiner in the rejection of claim 14, by specifying that the heavy and light chains correspond to those in anti-NGF monoclonal antibody αD11. This antibody is described in Cattaneo et al., 1988, J. Neurochem. 50: 1003-1010, as referenced in the specification (see page 6, line 33, into page 7).

Amended Claim 15 is directed to a transgenic mouse according to claim 14, wherein the anti-NGF antibody produced is a chimeric antibody, and specifies that the variable heavy chain is linked to a human γ1 constant region and the variable light chain is linked to a human k constant region.

9. Rejections under 35 USC 112, 1st paragraph – Written Description & New Matter:

Claims 1, 3-9 and 11-19 stand rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement and as introducing new matter.

Claims 3-7, 9 and 17-18 have been cancelled, thus mooting the rejection as to these claims.

Applicants have carefully considered each of the reasons indicated for these rejections, and have amended claims 1, 8, 11-16 and 19 to obviate or overcome the rejections. In particular, claim 1 is now limited to a transgenic *mouse*, rather than a non-human transgenic animal. Further, claim 1 has been amended to define the transgenic mouse of the invention in terms of the neurodegenerative pathology that these mice develop as they become adults. In this regard, amended claim 1 replaces the phrase *"reminiscent of a human neurodegenerative syndromes, muscular atrophy or dystrophy, or immune disorders"* with *"said mouse having, or being predisposed to the development of, an adult neurodegenerative pathology characterized by the presence of: (a) abnormally processed amyloid precursor protein, (b) amyloid precursor protein and/or β-amyloid protein plaques in the CNS, (c) hyperphosphorylation of tau protein, (d) neurofibrillary tangles in the brain, (e) cholinergic deficit, (f) neuronal loss in the cortex of the brain, and (g) behavioral cognitive deficit."*

The foregoing amendments result in an independent claim that more particularly points out and distinctly claims the subject matter which applicants regard as their invention, and which is fully supported by the written description provided in the instant specification. All other pending claims subject to this rejection depend

upon amended claim 1, and have been amended to be in accordance with amended claim 1, as well as to more particularly point out and distinctly claim the subject matter which applicants regard as their invention. These amended dependent claims are also fully supported by the written description provided by the instant specification. The amended claims contain no new matter.

The transgenic mouse of the invention expresses the anti-NFG antibody in a manner which results in the development of a characteristic neurodegenerative pathology as the mouse matures into an adult. The hallmark features of the pathology include the recited phenotypic characteristics. The use of the language, *"said mouse having, or being predisposed to the development of, an adult neurodegenerative pathology ..."* is required in order to encompass the transgenic mouse of the invention regardless of whether it has matured into an adult or not, as the development of the adult neurodegenerative pathology as defined is inevitably realized, and thus immature mice may properly be said to be *"predisposed to the development of"* the neurodegenerative pathology. This amendment does not introduce new matter, as one of skill in the art would understand that immature transgenic mice of the invention are predisposed to the pathology by design.

10. Rejections under 35 USC 112, 1st paragraph – Scope of Enablement:

Claims 1, 3-9 and 11-19 stand rejected under 35 USC 112, first paragraph, on the grounds that the specification does not reasonably provide enablement as specified.

The Office affirmatively states that the specification does provide enablement for a transgenic mouse that expresses the heavy and light chains of an anti-NGF

antibody, wherein the mouse has one or more of the phenotypic characteristics listed by the examiner and recited in the specification.

Applicants respectfully submit that amended claims 1, 8, 11-16 and 19, and new claims 38-45 are fully consistent with the Office's assessment on the issue of enablement.

11. Rejections under 35 USC 102(a):

claims 1, 3-9 and 11-19 stand rejected under 35 USC 102(a) as being anticipated by the following publications:

(i) Ruberti et al, 2000, J. Neuroscience 20(7): 2589-2601. Ruberti et al., 2000 was published April 1, 2000.

(ii) Capsoni et al., 2000, J. Neuroscience Res. 59: 553-560. Capsoni et al., 2000, J. Neuroscience was published February 15, 2000.

(iii) Capsoni et al., 2000, PNAS USA 97(12): 6826-6831. Capsoni et al., 2000, PNAS was published June 6, 2000.

Applicants submission of the replacement verified and sworn priority documents have satisfied the examiner's requirements for the same, and are otherwise in accordance with the Rules relating to translations of foreign priority documents.

Applicants respectfully submit that the translated priority documents now of record establish applicants' entitlement to the effective filing date of August 6, 1999 - the filing date of priority document MI99A001783. All three references cited by the Office were published after applicants effective filing date and do not constitute prior art. Accordingly, these three rejections should now be withdrawn.

12. Rejections under 35 USC 102(b):

Claims 1, 3-9 and 11-18 stand rejected under 35 USC 102(b) as being anticipated by Cattaneo 1996. The rejection is now moot as to cancelled claims 3-7, 9 and 17-18. Claims 1, 8 and 11-16 have been amended and have been discussed above.

The examiner indicates that the phenotypic change in the transgenic mice described in Cattaneo 1996, namely a 30% reduction in neurons of the superior cervical ganglia, is a characteristic considered to be reminiscent of neurodegenerative diseases. On the grounds that the transgenic mice of Cattaneo 1996 express an anti-NGF antibody constructed from the same heavy and light chain genes utilized in the generation of the transgenic mice of the invention, the examiner states that the genetic structures of these transgenic mice are indistinguishable, and that they comprise an identical transgene, concluding that claim limitations not specifically disclosed by Cattaneo 1996 are considered to be inherent in the transgenic mouse of Cattaneo 1996.

The Declaration of Antonino Cattaneo submitted herewith is offered as evidence in rebuttal. Applicants kindly request a thorough consideration of the Declaration.

In his Declaration, Prof. Cattaneo explains that the transgenic mouse of Cattaneo 1996 and the transgenic mouse of the invention have different phenotypes and genetic architectures, and are therefore not the same. Prof. Cattaneo's evidence clearly establishes, *inter alia*, the following:

(i) The mouse of the invention is generated using parental crosses that are different from the cross that was used to generate the transgenic mouse of Cattaneo et al 1996 [Cattaneo Declaration, paragraphs 4-6];

(ii) The expression levels of the anti-NGF antibody produced by the mouse of Cattaneo 1996 are substantially lower than the levels expressed by the mouse of the invention, and the antibody expression profiles also differ [Cattaneo Declaration, paragraphs 4, 8];

(iii) The presumption that the genetic structures of the mouse of the invention and the mouse of Cattaneo 1996 are indistinguishable is incorrect, as the physical location of the integrated transgenes within mouse chromosomal DNA differs between the two transgenic mice, and results in divergent antibody expression profiles and phenotypes. Thus, the genetic architectures of the two mice (and their respective parents) are not the same, and on that basis the mice are genetically distinguishable [Cattaneo Declaration, paragraphs 11-13; and,

(iv) The phenotype of the mouse of the invention is actually not present in the mouse of Cattaneo 1996, and it cannot be considered to be inherently present. [Cattaneo Declaration, paragraph 4, 11, 13].

The evidence now of record is clear and compelling, and strongly supports a conclusion that the transgenic mouse described in Cattaneo et al 1996 does not anticipate the claimed invention. Accordingly, this rejection should not be maintained.

13. Rejections under 35 USC 103(a):

Claims 1 and 17-19 were rejected under 35 USC 103(a) as being unpatentable over Cattaneo 1996 in view of Hogan et al. 1986. The rejection is now moot as to cancelled claims 17-18. Claims 1 and 19 have been amended and have been discussed above.

The Cattaneo Declaration submitted herewith is offered as evidence in rebuttal. Applicants submit that the evidence provided by Prof. Cattaneo refutes any notion that the claimed transgenic mouse of the invention is obvious. The evidence establishes, *inter alia,* that:

(i) There was no suggestion or motivation in Cattaneo 1996 to make the claimed transgenic mouse [Cattaneo Declaration, paragraphs 4, 9];

(ii) The particular crosses required for generating the transgenic mouse of the invention were not disclosed in Cattaneo et al., 1996, and were not predictable before the invention was made [Cattaneo Declaration, paragraphs 9-10];

(iii) The generation of a transgenic mouse having phenotypic characteristics resembling those seen in Alzheimer's Disease was an unexpected and surprising result [Cattaneo Declaration, paragraph 7];

(iv) Prior to the invention, there was no comprehensive transgenic model for Alzheimer's Disease. The prior art had shown that genetic disruption of the NGF gene in transgenic mice was lethal to the mice (Crowley et al., 1994), and that transgenic mice

expressing anti-NGF antibody only produced a modest decrease in neurons of the superior cervical ganglia (Cattaneo et al., 1996). [Cattaneo Declaration, paragraphs 4, 17];

(v) The model of the invention is the first and most comprehensive model for AD in the world, removing an obvious limitation in the study of AD [Cattaneo Declaration, paragraph 18]; and,

(vi) The invention has achieved commercial success. The invention was instrumental in the formation of Lay Line Genomics (LLG), the exclusive licensee of the applicant. Further, the invention is the subject of collaborative and licensing agreements with major pharmaceutical companies, and has generated revenue for LLG, clearly establishing a recognition of the model's value in the field of AD and neurodegenerative disease research. [Cattaneo Declaration, paragraph 20]

The invention is presently defined in the claims to be a transgenic mouse that has, or is predisposed to the development of, an adult neurodegenerative pathology characterized by the presence of: (a) abnormally processed amyloid precursor protein, (b) amyloid precursor protein and/or β-amyloid protein plaques in the CNS, (c) hyperphosphorylation of *tau* protein, (d) neurofibrillary tangles in the brain, (e) cholinergic deficit, (f) neuronal loss in the cortex of the brain, and (g) behavioral cognitive deficit.

Cattaneo 1996 is completely silent on the above features of the invention, and provides no suggestion that the transgenic mouse of the invention is possible, or provides any indication of how one would produce such a mouse. Hogan et al. 1986 does not supply the deficiencies of Cattaneo 1996.

The basic requirements of a *prima facie* case of obviousness are not met in this case. First, there is no suggestion or motivation in either of the cited references to make the invention. Second, there was no expectation of success – indeed, there could not have been, since the invention was unpredictable, and "success" was therefore not something that could be defined prior to the unexpected development of the invention. Third, the phenotypic claim limitations are not taught or suggested in the prior art.

The invention was surprising, unexpected and not predictable before the invention was made. The transgenic mouse of the invention revealed activities of NGF that were not known prior to the invention, and has become a useful and recognized model of AD.

Thus, the record also provides strong objective evidence of nonobviousness, as the facts establish that the invention was unexpected, that it satisfied a long felt need for a model of AD, and that it directly resulted in commercial success.

14. Additional Matter Raised by the Examiner:

On page 24 of the Office Action, last paragraph, the examiner indicates that if applicants provided proof that the mouse of Cattaneo 1996 did not have the claimed phenotype, this would constitute evidence of the unpredictability of the phenotype of the claimed transgenic mice. The examiner further indicates that, *"since there is no discernable difference in the structure of the mice, and no guidance as to how to reproducibly make the parental mice of the invention, instead of the parental mice of Cattaneo (1996), it would appear that the parental strains would have to be deposited...in order to enable claims to a mouse made by crossing those specific lines."*

A formal rejection for lack of enablement on this basis has not been made. However, in an effort to expedite prosecution of this application and avoid such a rejection, applicants take this opportunity to remark on the above, and provide the Office with evidence for the reproducibility of the invention.

Firstly, applicants have provided evidence that there is, indeed, a discernable difference in the structure of the mice. See remarks in paragraph 12, above.

Secondly, applicants wish to point out that the specification contains specific guidance on how to make the invention, including working examples demonstrating the generation of the required parental lines as well as the multiple crosses that generate the claimed invention.

Thirdly, Prof. Cattaneo's evidence is also offered to avoid a requirement for depositing the parental transgenic strains. Prof. Cattaneo provides strong evidence to support a conclusion that the claimed invention is fully reproducible and that the specification provides ample guidance to enable one of skill in the art to generate the required single transgene parental strains and use them to make a double transgenic mouse of the invention. See, in particular, paragraphs 9-10, 12 and 14-16 therein. To summarize, the evidence of record establishes, *inter alia*, the following:

(i) Variability in the level of expression of a given transgene in multiple founder mice is the result of the randomness of transgene integration into chromosomal DNA, as is well known in the art. Therefore, even using a relatively small number of founder mice, one will find high, medium and low expressors. [Cattaneo Declaration, paragraph 14, in view of explanations provided in paragraph 12];

(ii) Variability in expression levels from one founder transgenic animal to the next is an asset in the context of reproducing the invention. Using the specific teachings of the invention, this variability allows for the multiple combinations of high and low expressing parental transgenes required to reproduce the invention. [Cattaneo Declaration, paragraph 14, in view of paragraphs 5-10];

(iii) The specification teaches that crossing a parental mouse expressing high levels of either the heavy of light chain, with a parental mouse expressing low levels of the cognate chain, is the combination that leads to the development of the AD phenotype. [Cattaneo Declaration, paragraph 10];

(iv) Reproducing the homozygous parental lines needed to generate the transgenic mouse of the invention is enabled by the specification, and is well within the ordinary level of skill in the art, following the procedures outlined in Example 1 of the specification. Following the teachings of the invention, crosses between a high expressing heavy or light chain mouse, and a low expressing light or heavy chain mouse, respectively, will lead to the double transgenic mouse of the invention, which may be identified by screening for the characteristic phenotype, as described in Example 2 and elsewhere in the specification. [Cattaneo Declaration, paragraphs 14-15]; and,

(v) The fact that two different families of double transgenic mice, made using both combinations of high/low expressing–heavy chain/light chain parental mice, show the phenotype of the claimed invention, rules out integration-dependent effects and provides further

evidence of the reproducibility of the invention. [Cattaneo Declaration, paragraph 16]

In view of the foregoing, and the detailed teachings contained within the specification, applicants submit that the claimed invention is enabled within the meaning of 35 USC 112, 1st paragraph. Accordingly, applicants respectfully submit that a deposit is not required in this case, and respectfully request that no such requirement be made.

15. CONCLUSION:

Applicants have been as diligent and thorough as possible in preparing this response to the Office Action. In view of the foregoing amendments and submissions, the evidence provided by Prof. Cattaneo, and the foregoing remarks presented in reply to the Office Action, applicants kindly request a careful reconsideration of all pending objections to the specification, drawings, translations of priority documents, sequence listing, and all rejections of the claims. Applicants respectfully request withdrawal of the objections and rejections of record, and an early indication of allowance.

Respectfully submitted,

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Kenneth K. Sharples Reg. No. 35,355

Law Office of Kenneth K. Sharples
125 East Palace Avenue – Suite 54
Santa Fe, New Mexico 87501
Tels. 505 699 6688 & 505 466 0756
Fax. 505 983 2801
eMAIL k.sharples@att.net